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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/076,248	02/12/2002	Lloyd G. Mitchell	A31304-B-A-F 069906.0105	6317

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EXAMINER	
WILDER, CYNTHIA B	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 08/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/076,248	MITCHELL ET AL.	
	Examiner	Art Unit	
	Cynthia B. Wilder, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34 and 36-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-34 and 36-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)

2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3)☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 5/24/05

4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5)☐ Notice of Informal Patent Application (PTO-152)

6)☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed May 24, 2005 is acknowledged and has been entered. Claims 31-34, 48, 49 and 53 have been amended. Claim 35 has been canceled. Claims 54-60 have been added. All of the arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Priority

3. Applicant's amendment to the specification to change the priority document from 60/008317 to 60/008717 is acknowledged. However, it is noted that the oath or declaration does not recited the provisional application 60/008717 but rather recites 60/008317. A review of the continuation application 08/766354 from which the provisional application depends, confirms that the correct provisional application is indeed 60/008717 and the previous listing may have inadvertently been a typo. However, to clarify the record for the instant application a new oath or declaration is required because the provisional application as now amended on the first page of the specification and the provisional application listed on the oath or declaration are not the same. The wording of an oath or declaration cannot be amended. If the wording is not correct or if all of the required affirmations have not been made or if it has not been properly subscribed to, a new oath or declaration is required. The new oath or declaration must properly identify the application of which it is to form a part, preferably by application number and filing date in the body of the oath or declaration. See MPEP §§ 602.01 and 602.02.

Previous objections and rejections

4. The objections to claims 31-34, 48, 49 and 53 for improper multiple dependency in withdrawn in view of Applicants' amendment to the claims. The rejection under 35 USC 112 first paragraph as lacking enablement is maintained and discussed below. The rejection under 35 USC 112 first paragraph as lacking adequate written description is withdrawn in view of Applicant's arguments. The double patenting rejection is withdrawn in view of Applicant's submission of a proper terminal disclaimer.

Claim Rejections - 35 USC § 112

5. Once again claims 1-30, 36-47, 50-52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for producing chimeric RNA molecule using the modified synthetic nucleic acids molecules in a cell *in vitro*, it does not reasonably provide enablement for producing chimeric RNA molecules using the modified synthetic nucleic acid molecules *in vivo* for therapeutic treatment of various diseases and conditions and regulation of gene expression in a cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims, for the reasons of record in the Office action mailed 24 January 2005.

Applicant's traversal

6. Applicant traverses the rejection on the following grounds: Applicant summarizes cases law concerning the test for enablement and states that Applicant has published working examples of in vivo trans-splicing to produce a chimeric RNA, prior to the filing date of the present

application. Applicant states that in particular, PTM expression plasmids ere injected into tumors of athymic (nude) mice. Applicant states that the tumor were established by injecting H1299 cells (human lung cancer tumor cells) into the dorsal flank subcutaneous space of the mouse, PTM expression plasmid were then injected into the tumor and, after 48 hours, transplicing was detected in 8 out of 19 PMT-treated tumors, with two of the samples producing the predicted trans-splicing product. Applicant argues that six additional tumors were subsequently positive for transplicing, after a second PCR amplification, and again produced predicted trans-spliced product. Each positive sample was sequenced; demonstrating that betaHCG6 exon 1 was precisely trans-spliced to the coding sequence of DT-A at the predicted splice sites. Applicant contends that the disclosure of the present invention would enable one skilled in the art to make or use the claimed nucleic acids and cells in vivo, without undue experimentation. Applicant further asserts that an in vitro example in the specification constitutes a working example, sufficient to support enablement disclosure of the claimed nucleic acid and cells in vivo, if the example correlates with the claimed invention. Applicant summarizes the cited reference of Putteraju et al and argues that Puttaraju et al discloses that the mechanism of splicesome-mediated trans-splicing is the same whether it occurs in vivo or in vitro. Applicant states as a result, one skilled in the art would recognize a correlation between the results obtained using in vitro models and that expected in vivo. Applicant concludes that the in vitro models disclosed in the specification provides sufficient evidence of in vivo efficacy of the present invention. Applicant further summarizes disclosure from the specification and states that based on the teaching in the specification reconsideration and withdrawal of the rejection is requested.

Examiner's Response

6. All of the arguments have been thoroughly reviewed and considered but they are not found persuasive for the reasons that follow: In regards to Applicant's arguments concerning the publications which supports the instant disclosure being enabling prior to the filing date of the application, the Examiner acknowledges the publication but notes that the instant application claims priority back to December 15, 1995 and at the time the invention was made, the state of the prior art indicated that efficient delivery and expression of foreign DNA was not yet achieved by any method (Marshall, Science, 269: 1050-1055, August 1995). Nonetheless, even if Applicant's publication is assumed to be valid, the teaching in the references are not depicted by or disclosed in the instant specification. There is no enabling disclosure in the instant application which discloses an in vivo model of transplicing in nude mouse using electroporation to facilitate plasmid delivery. The teaching set forth in the Puttaraju references were not incorporated into the body of the specification as originally filed and it remains that the instant inventions read on methods of gene therapy in any cell type, any tumor or tissue type and any type of mammalian patient or cell, including humans. Further, neither Applicant's arguments nor specification provides a suffcient correlation between the *in vitro* production of chimeric RNA molecules using the PTMS of the instant invention and the production of a therapeutic effect in a human. Moreover, the Applicants have not provide a clear correlation between trans-splicing *in vitro* and the production of *in vivo* therapeutic effects. As stated in the prior Office Action, Applicant has not provide any clear guidance as to how to overcome the various factors that are known in the art to complicate the gene therapy art, i.e., the expression of the nucleic acid molecules of the invention for therapeutic purposes. To reiterate, "t]here are a variety of

factors that complicate the gene therapy art which have not been overcome by routine experimentation. Theses include the fate of the DNA vector itself (volume distribution, rate of clearance into the tissues, etc.) the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of MRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced and the proteins compartmentalization within the cells, or its secretor fate, once produced. Theses factors differ dramatically based on the vector used, the protein being produced, the subject it is administered to and the diseased being treated." Applicants have not addressed these factors, nor have they discussed how the specification as filed can be used as a guide to overcome these factors. Likewise, the claims as written broadly encompass methods such as gene therapy for a synthetic molecule, including ribozymes introduction into cells. The claims also encompass the use of the method in any cell type, in any tumor or tissue type, and any type of mammalian patients. Further, the cells undergoing a test may be subject to any of a variety of different conditions depending upon the particular patient studied, with insulin dependent patients for example receiving daily doses of a compound with significantly alters cellular metabolism while cancer patients may be receiving chemotherapeutic treatments, pain medicine for surgery, corticosteroids to reduce trauma associated with surgery which themselves significantly impact cellular metabolism or any of number of other complicating factors which would impact the ability of the synthetic molecule to correct the detect. All of these factors are encompassed by the "*in vivo* uses" of the instant invention which Applicant has not described in the specification as originally filed.

While the Examiner again acknowledges the teachings of Puttaraju et al, which has been provided by Applicant's as evidence of enablement, it is noted that the cited supports of Puttaraju et al further do not provide support commensurate fully in scope with the claims. As stated in the prior Office Action and noted above, the quantity of experimentation required to practice the claimed invention would encompass determining means such that all pre-trans splicing molecules are all expressed in the same diseased cells at the same time and for a sufficient period of time such that the desired chimeric mRNA molecule is produced in a therapeutic amount to correct the defect in a diseased cells. To practice the invention fully commensurate fully, the skilled artisan would have to devise means such the pre-trans splicing molecules are present in the appropriate cells, such that when the target pre-mRNA is produced the PTMs are available to utilize the cell's splicing machinery to produced the chimeric molecules of the present invention, wherein the chimeric molecules function to produce the therapeutic benefit in any cell type under any condition state.

In regards to Applicants' arguments that the mechanism of splicesomes-mediated transplicing to produce RNA is the same whether it occurs *in vivo* or *in vitro*, the Examiner agrees with Applicant. However, it is again noted that Applicants have not provided a clear correlation between transplicing *in vitro* to correct CFTR binding domains and the production of *in vivo* therapeutic effects. Although the mechanism may be the same, contrary to Applicant's assertion how to deliver the appropriate vectors expression PTMS to the appropriate tissues, at the appropriate time for a sufficient duration and concentration to correct a genetic defect and thereby produce a desired therapeutic effect has not been fully established. Again it is noted that Applicants have not provided any guidance as to how to overcome the various factors that

are known in the art to complicate the gene therapy art, i.e., the expression of the nucleic acid molecules of the invention for therapeutic purposes. Therefore, it is concluded that the amount of experimentation required for the skilled artisan to practice the full scope of the claimed invention would be undue based upon the known unpredictability regarding the efficient delivery of gene therapy constructs *in vivo* in any cell type and further with the production of secondary effects, such as treating a diseases associated with the expression of a gene, and the lack of guidance in the specification as filed in this regard. The quantity of experimentation required to practice the invention as claimed would require determining modes of delivery in any and every cell type including a whole organism, such a human such that the expression of a single gene is replaced and the desired secondary effect (treating a patient with a diseases associated with the expression of a gene) is obtained. The specification as filed provides no specific guidelines in this regard. The quantity of experimentation required is also large because there is significant variability in the efficacy of gene therapy. The amount of experimentation necessary to solve the problems associated with *in vivo* uses of synthetic molecules, including ribozymes, which are encompassed by the instant invention, is very substantial requiring extensive animal and human experimentation with numerous non-obvious improvements likely to be necessary in order to achieve functionality, safety and efficacy of the compound in an *in vivo* organismal setting. This would require years of inventive efforts, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps. Therefore, for all of the foregoing reasons, the rejection under 35 USC 112 first paragraph is maintained.

New Grounds of Rejections

Claim Rejections - 35 USC § 112 second paragraph: Indefiniteness

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1- 34 and 36-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 1-34 and 36-49 lack proper antecedent basis in claims 1-3, 16-18 and 36-38 at step (a) for the limitation "the cell" because the preamble or any preceding steps do not recite "a cell". It is suggested changing "the" to "a" such that the claims language agree.

Claim Rejections - 35 USC § 112 first paragraph: Enablement

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 31-34, 48, 49 and 54-60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for producing chimeric RNA molecule using the modified synthetic nucleic acids molecules in a cell *in vitro*, it does not reasonably provide enablement for producing chimeric RNA molecules using the modified synthetic nucleic acid molecules *in vivo* for therapeutic treatment of various diseases and conditions and regulation of gene expression in a cell. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The first paragraph of section 112 requires the specification describe how to make and use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is "undue". These factors include but are not limited to: (1) quantity of experimentation necessary, (2) the amount of direction or guidance presented in the specification, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability of the unpredictability of the art and (8) the breadth of the claims. (See *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404, (Fed. Cir. 1988)) *(MPEP 2164.01(a))*.

Breadth of the claims and Quantity of Experimentation Necessary

The instant invention is drawn to a modified synthetic nucleic acid molecule, composition and method of producing chimeric RNA, wherein said molecule, composition and method comprises a modified synthetic nucleic acid comprising: one or more target binding domains that target binding of the nucleic acid molecule to a pre-mRNA expressed within the cell; a 3' spliced region comprising a branch point, a pyrimidine tract and a 3' splice acceptor site or a 5' splice site and a nucleotide sequence to be trans-spliced to be target pre-mRNA; wherein said nucleic acid molecule is recognized by nuclear splicing components within the cell, wherein said cell encompasses cells in a whole organism. The specification as filed provides only sufficient guidance and/or instruction for using the claimed synthetic nucleic acid construct to produce chimeric molecules within a cell in an *in vitro* environment, wherein said constructs are

used to produce a chimeric mRNA. The specification as filed does not provide sufficient guidance such that the ordinary skilled artisan could use the teachings of the specification as filed as a guide to use the compounds of the instant claims to treat various diseases and conditions in a method of gene therapy. Likewise, the claims as written broadly encompass methods such as gene therapy for a synthetic molecule, including ribozymes introduction into cells. The claims also encompass the use of the use of the method in any cell type, in any tumor or tissue type, and any type of mammalian patients. Further, the cells undergoing a test may be subject to any of a variety of different conditions depending upon the particular patient studied, with insulin dependent patients for example receiving daily doses of a compound with significantly alters cellular metabolism while cancer patients may be receiving chemotherapeutic treatments, pain medicine for surgery, corticosteroids to reduce trauma associated with surgery which themselves significantly impact cellular metabolism or any of number of other complicating factors which would impact the ability of the synthetic molecule to correct the detect. All of the factors are encompassed by the "in vivo uses" of the instant invention which have not been addressed by the instant invention as originally filed.

The art teaches that there are a variety of factors that complicate the gene therapy art which have not been overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, et), the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount of stability of the protein produced, and the protein's compartmentalization

within the cell, or its secretory fate, once produced (see Ech and Wilson (Goodman & Gilman's The Pharmacological Basis of Therapeutics, Ninth Edition, McGraw-Hill, New York, pages 77-101, 1996). These factors differ dramatically based on the vector used, the protein being produced the subject it is administered to, and the diseased being treated. Applicant does not address these factor nor does the specification provide any guidance to the skilled artisan on how to make and use genetic constructs that would result in the desired effect. Even assuming that an effective genetic material is constructed, it is not evident that enough cells can be transfected to provide any therapeutic benefits in any cell type under any variable conditions. Thus the quantity of experimentation required is large since there is significant variability in the efficacy of gene therapy. The amount of experimentation necessary to solve the problems associated with in vivo uses of synthetic molecules, including ribozymes which are encompassed by the instant invention, is very substantial requiring extensive animal and human experimentation with numerous non-obvious improvements likely to be necessary in order to achieve functionality, safety and efficacy of the compound in an in vivo organismal setting. This would require years of inventive efforts, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps. Thus, undue experimentation would be required to practice the claimed invention.

Unpredictability of the art and the state of the prior art

It is noted that the instant application claims priority back to December 15, 1995. However, it is noted that at the time the instant invention was made, the state of the prior art indicated that efficient delivery and expression of foreign DNA has not yet been achieved by any method. Marshall (Science. Vol. 269, pages 1050-1055, August 1995) states "there has been no

unambiguous evidence that genetic treatment has produced therapeutic benefits" (page 1050, col. 1) and that "difficulties is getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field" (page 1054, col. 3). James Wilson, one skilled in the art, is quoted in the Marshall article as saying that "[t]he actual vectors- how we're going to practice our trade- haven't been discovered yet" (page1055, col. 2).

In the instant case, the quantity of experimentation required to practice the claimed invention would encompass determining means such that all pre trans-splicing molecules are all expressed in the same diseased cells at the same time and for a sufficient period of time such that the desired chimeric mRNA molecule is produced in a therapeutic amount to correct the defect in the diseased cells. Neither the specification as filed, nor the state of the prior art at the time the invention was made provides any specific guidelines in this regard. The deficiencies in specification would constitute undue experimentation since theses steps must be achieved without instruction from the specification before one is enable to practice the claimed invention.

Working Examples

The specification has no working examples of *in vivo* treatment in any cell type or under any varied condition. The examples are based on *in vitro* analysis using the synthetic nucleic acid molecules.

Guidance in the Specification

The specification, while suggesting the use of the molecules of the instant invention *in vivo,* the specification does not provide significant guidance on how to overcome art recognized problems noted above. Accordingly, adequate guidance is not provided.

Level of skill in the art

The level of skill in the at is deemed high.

Conclusion

Therefore, it is conclude that the amount of experimentation required for the skilled artisan to practice the full scope of the claimed invention would be undue based upon the know unpredictability regarding the efficient delivery of gene therapy constructs *in vivo* and further with the production of secondary effects such as treating a disease associated with the expression of a gene, and the lack of guidance in the specification as filed in this regard. The quantity of experimentation required to practice the invention as claimed would require determining modes of delivery in a whole organism such that the expression of a single gene is replaced and the desired secondary effect is obtained. To reiterate, the specification as filed provides no specific guidelines in this regard. The deficiency in the specification would constitute undue experimentation sine these steps must be achieved without instructions from the specification before one is enable to practice the claimed invention.

Double Patenting

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. ' Claims 1-33, 36-47 and 50-60 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 6083702. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F. 2d 887, 225 USPQ 645 (fed. Cir. 1985).

Although the conflicting claims are not identical, they are not patentably distinct from each other. Instant claims 1-33, 36-47 and 50-60, and the claims 1-27 of US. Patent No. 6083702 are both directed to a nucleic acid comprising one or more target binding domains that target binding of the nucleic acid to a pre-mRNA expressed within a cells; a 3' spliced region comprising a branch point, a pyrimidine tract and a 3' spliced acceptor site; a 5' splice site; and a nucleotide sequence to be trans-spliced to the target pre-mRNA; wherein said nucleic acid molecule is recognized by nuclear splicing components within the cell and expression vector which expresses a nucleic acid molecule comprising the components listed above and method of producing a chimeric RNA comprising the nucleic acid molecule The claims only from each other in that the claims of the instant application recite wherein the nucleic acid molecules are modified and synthetic whereas the claims of the US patent recite nucleic acid molecules or recite "a cell comprising the nucleic acid molecule" instead of "the synthetic, modified nucleic acid molecule within a cell" as claimed . Thus, the claims 1-34, 36-47 and 50-60 of the instant invention falls entirely within the scope of the claims 1-27 of US patent 6,013,487. As the court

stated in *In re Goodman*, 29 USPQ2d 2010 (CAFC 1993), " a second application-- "containing a broader claim, more generical in its character than the specific claim in the prior patent"-- typically cannot support an independent valid patent. Miller, 151, U.S. at 198; See Stanley, 214 F.2d at 153. Thus, the generic invention, as noted above is "anticipated" by the species of the patented invention. Cf., Titanium metal corp. v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (holding that an earlier species disclosure in the prior art defeats any generic claims). This court's predecessor has held that, without a terminal disclaimer, the species claims preclude issuance of the generical application. "*In re Van Ornum*, 686 F.2d 937, 944, 214 USPQ 761, 767 (CCPA 1982); *Schneller*, 397 F.2d at 354".

13. Claims 1-34, 36-47 and 50-60 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, 9-18, 28-32 of U.S. Patent No. 6280978. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F. 2d 887, 225 USPQ 645 (fed. Cir. 1985).

Although the conflicting claims are not identical, they are not patentably distinct from each other. Instant claims 1-34, 36-47 and 50-60, and the claims 1-6, 9-18, 28-32 of U.S. Patent No. 6280978. The claims are both directed to a nucleic acid comprising one or more target binding domains that target binding of the nucleic acid to a pre-mRNA expressed within a cells;

a 3' spliced region comprising a branch point, a pyrimidine tract and a 3' spliced acceptor site; a 5' splice site; and a nucleotide sequence to be trans-spliced to the target pre-mRNA; wherein said nucleic acid molecule is recognized by nuclear splicing components within the cell and expression vector which expresses a nucleic acid molecule comprising the components listed above and method of producing a chimeric RNA comprising the nucleic acid molecule The claims only from each other in that the claims of the instant application do not recite wherein the target binding domain targets a CFTR pre-mRNA expressed within the cell. However, the claims of the instant invention broadly encompasses "any target binding domain to a pre-mRNA within a cell". Thus, the claims 1-34, 36-47 and 50-60 of the instant invention falls entirely within the scope of the claims 1-6, 9-18, 28-32 of U.S. Patent No. 6280978. As the court stated in *In re Goodman*, 29 USPQ2d 2010 (CAFC 1993), " a second application-- "containing a broader claim, more generical in its character than the specific claim in the prior patent"-- typically cannot support an independent valid patent. Miller, 151, U.S. at 198; See Stanley, 214 F.2d at 153. Thus, the generic invention, as noted above is "anticipated" by the species of the patented invention. Cf., Titanium metal corp. v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (holding that an earlier species disclosure in the prior art defeats any generic claims). This court's predecessor has held that, without a terminal disclaimer, the species claims preclude issuance of the generical application. "*In re Van Ornum*, 686 F.2d 937, 944, 214 USPQ 761, 767 (CCPA 1982); *Schneller*, 397 F.2d at 354".

14. Claims 1-34, 36-47 and 50-60 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-51 of U.S.

Patent Application 09/756,096. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F. 2d 887, 225 USPQ 645 (fed. Cir. 1985).

Although the conflicting claims are not identical, they are not patentably distinct from each other. Instant claims 1-34, 36-47 and 50-60, and the claims 1-51 of US. Patent Application No. 09/756096 are both directed to a nucleic acid comprising one or more target binding domains that target binding of the nucleic acid to a pre-mRNA expressed within a cells; a 3' spliced region comprising a branch point, a pyrimidine tract and a 3' spliced acceptor site; a 5' splice site; and a nucleotide sequence to be trans-spliced to the target pre-mRNA; wherein said nucleic acid molecule is recognized by nuclear splicing components within the cell and expression vector which expresses a nucleic acid molecule comprising the components listed above and method of producing a chimeric RNA comprising the nucleic acid molecule. The claims only from each other in that the claims of application 09/756096 recites "a nucleic acid molecules " whereas the claims of the instant invention recites " a synthetic, modified nucleic acid molecule". Thus, the claims 1-34, 36-47 and 50-60 of the instant invention falls entirely within the scope of the claims 1-51 of US. Patent Application No. 09/756096. As the court stated in *In re Goodman*, 29 USPQ2d 2010 (CAFC 1993), " a second application-- "containing a broader claim, more generical in its character than the specific claim in the prior patent"-- typically cannot support an independent valid patent. Miller, 151, U.S. at 198; See Stanley, 214

F.2d at 153. Thus, the generic invention, as noted above is "anticipated" by the species of the patented invention. Cf., Titanium metal corp. v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (holding that an earlier species disclosure in the prior art defeats any generic claims). This court's predecessor has held that, without a terminal disclaimer, the species claims preclude issuance of the generical application. "*In re Van Ornum*, 686 F.2d 937, 944, 214 USPQ 761, 767 (CCPA 1982); *Schneller*, 397 F.2d at 354".

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

15. Claims 1-34, 36-47 and 50-60 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-23, 28-35 and 37-39 of U.S. Application No. 09941492. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F. 2d 887, 225 USPQ 645 (fed. Cir. 1985).

Although the conflicting claims are not identical, they are not patentably distinct from each other. Instant claims 1-34, 36-47 and 50-60, and the claims 1-23, 28-35 and 37-39 of U.S. Application No. 09941492. The claims are both directed to a nucleic acid comprising one or more target binding domains that target binding of the nucleic acid to a pre-mRNA expressed within a cells; a 3' spliced region comprising a branch point, a pyrimidine tract and a 3' spliced

acceptor site; a 5' splice site; and a nucleotide sequence to be trans-spliced to the target pre-mRNA; wherein said nucleic acid molecule is recognized by nuclear splicing components within the cell and expression vector which expresses a nucleic acid molecule comprising the components listed above and method of producing a chimeric RNA comprising the nucleic acid molecule The claims only from each other in that the claims of the instant application do not recite wherein the target binding domain targets a human papilloma virus pre-mRNA expressed within the cell. However, the claims of the instant invention broadly encompasses "any target binding domain to a pre-mRNA within a cell". Thus, the claims 1-34, 36-47 and 50-60 of the instant invention falls entirely within the scope of the claims 1-23, 28-35 and 37-39 of U.S. Application No. 09941492. As the court stated in *In re Goodman*, 29 USPQ2d 2010 (CAFC 1993), " a second application-- "containing a broader claim, more generical in its character than the specific claim in the prior patent"--typically cannot support an independent valid patent. Miller, 151, U.S. at 198; See Stanley, 214 F.2d at 153. Thus, the generic invention, as noted above is "anticipated" by the species of the patented invention. Cf., Titanium metal corp. v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (holding that an earlier species disclosure in the prior art defeats any generic claims). This court's predecessor has held that, without a terminal disclaimer, the species claims preclude issuance of the generical application. "*In re Van Ornum*, 686 F.2d 937, 944, 214 USPQ 761, 767 (CCPA 1982); *Schneller*, 397 F.2d at 354".

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

16. Claims 1-34, 36-47 and 50-60 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6, 9-23 and

28-34 of U.S. Application No. 09/838858 An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F. 2d 887, 225 USPQ 645 (fed. Cir. 1985).

Although the conflicting claims are not identical, they are not patentably distinct from each other. Instant claims 1-34, 36-47 and 50-60, and the claims 1-6, 9-23 and 28-34 of U.S. Application No. 09/838858. The claims are both directed to a nucleic acid comprising one or more target binding domains that target binding of the nucleic acid to a pre-mRNA expressed within a cells; a 3' spliced region comprising a branch point, a pyrimidine tract and a 3' spliced acceptor site; a 5' splice site; and a nucleotide sequence to be trans-spliced to the target pre-mRNA; wherein said nucleic acid molecule is recognized by nuclear splicing components within the cell and expression vector which expresses a nucleic acid molecule comprising the components listed above and method of producing a chimeric RNA comprising the nucleic acid molecule The claims only from each other in that the claims of the instant application do not recite wherein the target binding domain targets a factor VIII pre-mRNA expressed within the cell. However, the claims of the instant invention broadly encompasses "any target binding domain to a pre-mRNA within a cell". Thus, the claims 1-34, 36-47 and 50-60 of the instant invention falls entirely within the scope of the claims 1-6, 9-23 and 28-34 of U.S. Application No. 09/838858. As the court stated in *In re Goodman*, 29 USPQ2d 2010 (CAFC 1993), " a second application-- "containing a broader claim, more generical in its character than the specific

claim in the prior patent"--typically cannot support an independent valid patent. Miller, 151, U.S. at 198; See Stanley, 214 F.2d at 153. Thus, the generic invention, as noted above is "anticipated" by the species of the patented invention. Cf., Titanium metal corp. v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (holding that an earlier species disclosure in the prior art defeats any generic claims). This court's predecessor has held that, without a terminal disclaimer, the species claims preclude issuance of the generical application. "*In re Van Ornum*, 686 F.2d 937, 944, 214 USPQ 761, 767 (CCPA 1982); *Schneller*, 397 F.2d at 354".

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

17. Claims 1-34, 36-47 and 50-60 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8, 10-21 and 23-39 of US application 10/456,153. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F. 2d 887, 225 USPQ 645 (fed. Cir. 1985).

Although the conflicting claims are not identical, they are not patentably distinct from each other. Instant claims 1-34, 36-47 and 50-60, and the claims 1-8, 10-21 and 23-39 of US application 10/456,153. The claims are both directed to a nucleic acid comprising one or more target binding domains that target binding of the nucleic acid to a pre-mRNA expressed within a cells; a 3' spliced region comprising a branch point, a pyrimidine tract and a 3' spliced acceptor

site; a 5' splice site; and a nucleotide sequence to be trans-spliced to the target pre-mRNA; wherein said nucleic acid molecule is recognized by nuclear splicing components within the cell and expression vector which expresses a nucleic acid molecule comprising the components listed above and method of producing a chimeric RNA comprising the nucleic acid molecule The claims only from each other in that the claims of the instant application do not recite wherein the target binding domain targets a factor VIII pre-mRNA expressed within the cell. However, the claims of the instant invention broadly encompass "any target binding domain to a pre-mRNA within a cell". Thus, the claims 1-34, 36-47 and 50-60 of the instant invention fall entirely within the scope of the claims 1-8, 10-21 and 23-39 of US application 10/456,153. As the court stated in *In re Goodman*, 29 USPQ2d 2010 (CAFC 1993), " a second application-- "containing a broader claim, more generical in its character than the specific claim in the prior patent"-- typically cannot support an independent valid patent. Miller, 151, U.S. at 198; See Stanley, 214 F.2d at 153. Thus, the generic invention, as noted above is "anticipated" by the species of the patented invention. Cf., Titanium metal corp. v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (holding that an earlier species disclosure in the prior art defeats any generic claims). This court's predecessor has held that, without a terminal disclaimer, the species claims preclude issuance of the generical application. "*In re Van Ornum*, 686 F.2d 937, 944, 214 USPQ 761, 767 (CCPA 1982); *Schneller*, 397 F.2d at 354".

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Prior art

18. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Hasselof et al (US 5641673) teach a nucleic acid molecule comprising one or target binding domains of the a nucleic acid molecule to a pre-mRNA expressed with a cell, a 3' splice region and 5' splice region and splice acceptor sites and branch point and a nucleotide sequence to be trans-spliced to the target pre-mRNA. Hasselof et al do not teach a pyrimidine tract but rather requires the presence of guanosine cofactors.

Conclusion

19. No claims are allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia B. Wilder, Ph.D. whose telephone number is (571) 272-0791. The examiner works a flexible schedule and can be reached by phone and voice mail. Alternatively, a request for a return telephone call may be emailed to cynthia.wilder@uspto.gov. Since email communications may not be secure, it is suggested that information in such request be limited to name, phone number, and the best time to return the call.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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